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ORIGINAL ARTICLE

Tuberculosis despite latent infection screening and treatment in patients receiving TNF inhibitor therapy

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Abstract

Introduction Although latent tuberculosis infection (LTBI) treatment is given before anti-tumor necrosis factor (TNF) treatment, tuberculosis (TB) still develops in these patients and the risk factors are not well known. Besides, there is little data on the safety of isoniazid (INH) treatment in this group of patients. This study aimed to determine the risk factors for the development of tuberculosis and the safety of LTBI in such patients.

Methods All patients (n=665) given anti-TNF in a single center were included in this study. Complete data were obtained from the records of 389 patients.

Results Seven patients (1.1%) were diagnosed with TB. There was no significant difference in age, gender, smoking rate, comorbidities, leukocyte counts, hemoglobin, creatinine, AST, ALT, protein levels, and tuberculin reaction between patients with and without TB. Of 389 patients, 289 (76%) had received INH prophylaxis, including 43 tuberculin-negative patients. Thirty patients had anti-TNF use prior to INH prophylaxis. None of these patients had TB in the follow-up period. Seven patients who developed TB had completed LTBI treatment, including one patient who was tuberculin-negative. The time from the completion of INH treatment to the diagnosis of TB was 6–61 months. None had any history of contact with TB during this period. INH treatment was associated with hepatotoxicity in 49 patients (17%); all resolved without any need to stop INH.

Conclusion Patients on anti-TNF treatment had a high rate of TB despite INH prophylaxis, but no risk factor for TB development was identified. Mild hepatotoxicity frequently developed during LTBI treatment.

Key Points
- *Tuberculosis still develops in patients treated with tumor necrosis factor (TNF)–inhibitors despite prior screening and treatment for latent tuberculosis infection (LTBI).*
- *In this cohort, all patients in whom tuberculosis developed had been treated for LTBI and all but one were initially tuberculin-positive. No risk factors have been identified.*
- *The current policy of treating tuberculin-positive patients with a 9-month INH regimen does not seem to be fully effective in preventing tuberculosis.*

Keywords Hepatotoxicity · Isoniazid · TNF inhibitor · Treatment · Tuberculosis

Introduction

Tuberculosis is an important infection in immunosuppressed patients, particularly in countries where the prevalence is high [1]. Any condition or treatment that compromises cellular immunity is associated with an increased risk of developing tuberculosis.

The use of tumor necrosis factor (TNF) inhibitor drugs has led to significant improvements in the management of immune-related diseases, particularly the connective tissue diseases, with a consistent rise in the number of such patients to whom they are administered. One major drawback of the use of TNF inhibitor treatment is an increased risk of

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infections, particularly tuberculosis [2–5]. Tumor necrosis factor-alpha is involved in several immune processes, including the release of cytokines from the macrophages, resulting in the recruitment and activation of T-lymphocytes and formation and maintenance of granulomas [6]. Blocking the activity of TNF-alpha is thus expected and has been shown to be associated with an increase in the rate of tuberculosis and non-tuberculous mycobacterial disease.

Several local and international guidelines have thus recommended that patients who are candidates for anti-TNF treatment be screened for latent tuberculosis infection (LTBI) and be treated if they are found to be infected [7, 8]. The usual treatment consists of the administration of isoniazid (INH) for 9 months.

Previous observational studies have shown that tuberculosis still develops in patients receiving TNF inhibitor drugs despite their regular screening and treatment for LTBI at relatively high rates [9, 10].

The rates of tuberculosis in two previous studies from Turkey were 1.16 and 0.64%, resulting in annual incidences of 423 and 367/100.000 [9, 10], i.e., 21.3–24.6-fold higher than in the general Turkish population. Similarly, another study on Turkish patients with psoriasis receiving TNF-inhibitors showed that the rate and annual incidence of tuberculosis were 1.08% and 890/100.000, respectively [11]. Unfortunately, there are no published studies from Turkey reporting on the rate of tuberculosis prior to the implementation of LTBI screening and treatment, which precludes any direct comparison between pre and post-implementation periods. However, a study from Spain reported incidence rates of 1893 and 1113/100.000 in the years 2000 and 2001, respectively [12]. Thus, although the current strategy appears to have lowered the incidence rate of tuberculosis, the risk of tuberculosis is still substantially higher than in the general population. The question therefore arises whether the current strategy for screening and treating LTBI is valid and whether it needs reappraisal. However, one needs to consider that in the previous retrospective studies, the compliance of the patients to LTBI treatment was not known. Besides, different risk factors have been found in different studies and more data are clearly needed to define high-risk subgroups for whom alternative preventive approaches may be developed.

This study thus aimed to determine the risk factors for the development of tuberculosis in patients who have already been screened and treated for LTBI in a single referral center and to critically evaluate the effectiveness and safety of INH prophylaxis.

Patients and methods

This was a retrospective study that included all patients (n=665) receiving TNF inhibitor treatment between 2010 and 2016 at the Division of Rheumatology, Department of Internal Medicine. Patients followed up by other departments and receiving TNF inhibitor treatment for indications other than connective tissue diseases were not included.

The study was approved by the local Ethics Committee (approval no: 18-10/23) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All tuberculosis patients gave written informed consent prior to their inclusion in the study.

The hospital records of all the patients were examined including data on their demographics, primary diagnosis of rheumatologic disease and time since diagnosis, treatments received prior to the time of tuberculosis diagnosis, tuberculin reaction, history of previous tuberculosis or contact with patients with active tuberculosis, and follow-up of LTBI treatment.

All patients, except 30, had been screened for LTBI prior to the initiation of TNF inhibitor treatment and treated according to national and international guidelines. Thirty patients had started receiving TNF inhibitor treatment 3–17 months prior to the release of the national guidelines and were thus screened thereafter. All patients were screened with a chest x-ray and tuberculin skin test and were treated with isoniazid for 9 months if the tuberculin reaction size was 5 mm or larger, or they reported recent contact with a tuberculosis patient, or fibrotic opacities were present on their radiograms. The latter group was further examined for active tuberculosis with routine sputum examinations. A booster tuberculin test was not regularly performed because of low patient compliance. Interferon-gamma release assays were done in a minority of the patients as they were not regularly available in the hospital and were not reimbursed by the national insurance system. Tuberculin test was not performed at the time of diagnosis of tuberculosis.

A total of seven patients were found to have developed active tuberculosis despite receiving LTBI treatment. All seven patients were called to the outpatient clinic for a follow-up visit, at which a face-to-face interview was carried out to question their adherence to INH treatment and possible contact with cases of active tuberculosis following the completion of LTBI treatment.

Statistical analysis

The categorical variables were analyzed with frequency tables and descriptive statistics were used for the continuous variables. Pearson's chi-square test and Fisher's exact test were used for the analysis of categorical variables in groups. Shapiro-Wilk normality test was used to examine whether the numeric values had a normal distribution in groups. When the numeric values were not normally distributed, Mann-Whitney U test was used to compare the median values

of two independent groups.The level of significance was chosen as 0.05 in all hypothesis tests. IBM SPSS Version 25.0 statistical package was used for statistical analyses.

Results

Study population

A total of 665 patients were followed up during the study period and they were all included to determine the prevalence of active tuberculosis in this patient population. However, relevant data, e.g., detailed history, tuberculin reaction, and follow-up liver enzyme levels, lacked from the records of 276 patients, so the following analysis is based on data from the records of 389 patients.

A flowchart of the patient population is shown in Fig. 1. Of the 389 patients, 100 were tuberculin negative and were not treated for LTBI. Of the remaining 289 patients, 43 were tuberculin negative, but were given INH treatment at the discretion of the attending physician. Two hundred and forty-six patients were tuberculin positive and received LTBI treatment. As previously described, 30 patients had started receiving TNF inhibitor treatment prior to the release of the national guidelines and were screened thereafter. Of these 30 patients, 18 were found to be tuberculin positive and were then treated for LTBI. None of these 30 patients developed tuberculosis.

Seven patients (46.2±0.5 years, 4 females) developed tuberculosis (1.05%). Three had ankylosing spondylitis, two had psoriatic arthritis, and two had rheumatoid arthritis. Two patients had concomitant diabetes mellitus, two familial Mediterranean fever, the remaining three patients did not have any comorbidities.

Tuberculosis developed in six of the tuberculin-positive patients who had received LTBI treatment 6–61 months prior to the diagnosis. Besides, there was one tuberculosis patient who was tuberculin-negative, but who had still received INH treatment, possibly because she had fibrotic scars on her chest radiogram. In the control group of 382 patients, six (1.6%) had radiographic findings which would be compatible with past tuberculosis, i.e., apical fibrotic scars and/or calcified hilar lymph nodes (p=0.12).

Four patients had pulmonary tuberculosis. None of them was resistant to isoniazid. The remaining three patients had pathologically confirmed diagnoses of extrapulmonary tuberculosis (all lymph node tuberculosis) and did not have any resistance data.

All seven patients were interviewed face to face. They all confirmed to have completed 9 months of INH treatment, except for one patient who received INH for 8 months. None of the patients reported any contact to a tuberculosis case during or after

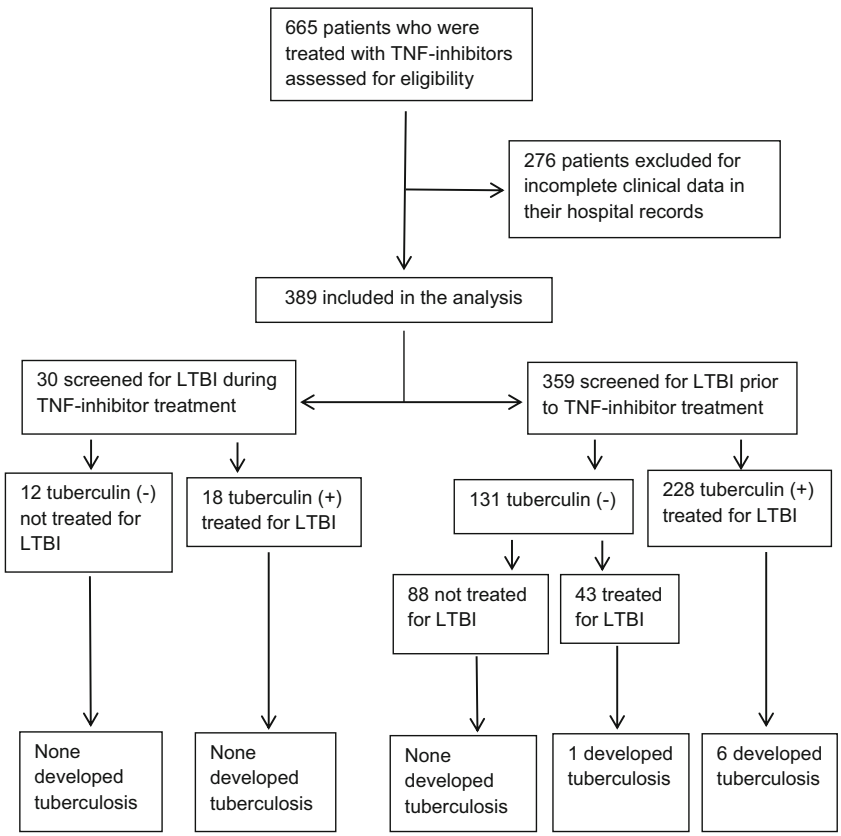

Fig. 1 Flowchart of the patient population

the LTBI treatment. None of them had any prior history of tuberculosis but one had radiographic evidence of possible past tuberculosis, namely apical fibrotic opacities. They were all ultimately successfully treated with the standard four-drug regimen and did not have any recurrence.

Patients who did and who did not develop tuberculosis were compared regarding their demographic features, laboratory findings, tuberculin reaction sizes, and the type and duration of their TNF inhibitor treatment and no differences were found (Table 1). Two patients each were receiving infliximab, adalimumab, and etanercept and one patient was receiving certolizumab at the time of diagnosis. Besides, four patients were treated with methotrexate, one with azathioprine, three with sulfasalazine, and four with low-dose prednisolone during the 6 months preceding the diagnosis. These were similar to the treatments given to patients who did not develop tuberculosis (n = 261 [68.3%], 51 [13.3%], and 103 [27.0%], for control patients receiving methotrexate, azathioprine, and low-dose steroids during the follow-up).

The hospital records of all 289 patients who received INH treatment were examined for their liver function during treatment. The levels of either or both of ALT and AST were found to have increased in 49 (17.0%) patients. All increases were less than 3-fold, there were no other signs or symptoms of hepatotoxicity, and there was no need to stop the INH treatment in any of the patients.

Discussion

This study showed that tuberculosis develops at a high rate in patients on TNF inhibitor treatment, despite appropriate screening for and treatment of LTBI. In this study population, the majority of the cases were initially tuberculin positive and had thus received the recommended 9-month INH treatment. No significant risk factors were identified, which may have been related to the relatively small number of cases. INH treatment was associated with mild hepatotoxicity, which may be of concern in patients with other risk factors.

A review of the literature shows that tuberculosis does develop in patients on TNF inhibitor treatment despite screening and treatment of LTBI. It has been reported to occur more commonly in patients with no initial evidence of LTBI [13–17], except for three previous studies from Turkey [9, 10, 18], in which tuberculosis developed more frequently in tuberculin-positive patients. This may, therefore, be related to the prevalence of tuberculosis infection and the inclusion of BCG in the pediatric immunization program.

It may be argued that screening for LTBI was not optimal in this cohort, as it was assessed with tuberculin skin test only and that no booster dose was given. This may have resulted in a fewer number of patients with LTBI and thus, a fewer number of patients to whom INH treatment was given. Besides, it has been reported that almost 5% of patients who had been previously screened and found to be tuberculin-negative were later found to be positive when re-tested [19]. However, although single-step tuberculin test results in lower rates of LTBI diagnosis, INH treatment based on a single-step test is not associated with an increase in the incidence of tuberculosis, i.e., a failure to prevent the disease [20]. Besides, the main issue in this study and in some of the previous studies [9, 10] was that tuberculosis also developed in patients who were initially tuberculin positive and who had received a full course of INH treatment. Some of the tuberculin-negative patients were also given INH treatment at the discretion of the attending physician, possibly due to concern for the low sensitivity

Table 1 Demographic, clinical, and laboratory findings in patients who did and who did not develop tuberculosis

	TB (+) (n=7)	TB (−) (n=382)	p
Age (years)	46.2±0.5	48.3±13.7	0.699
Gender (M/F)	3/4	206/176	0.766
White blood cells count (/μL)	6652.5±1686,1	7757.1±2056,8	0.127
Lymphocyte count (/μL)	1842.5±592	2192.8±753.6	0.245
Hemoglobin (g/dL)	12.6±1,6	13.0 ±2.0	0.433
Creatinine (mg/dL)	0.7±0,2	0.8±0.7	0.736
AST (U/L)	21.7±5.7	18.4±5.9	0.069
ALT (U/L)	21.6±6.6	18.7±10.5	0.154
Albumin (g/dL)	4.1±0.3	4.3±0.5	0.087
Total protein (g/dL)	7.5±0.6	7.3±0.6	0.284
Duration of anti-TNF treatment (months)a	22.6±18.7	49.1±37.8	0.084
Tuberculin reaction (mm)	12.2±7.6	7.5±5.8	0.112
Cigarette smokers (n, %)	1 (12.5)	176 (46.1)	0.074
Patients with comorbidities (n, %)	4 (50)	182 (47.6)	0.913

[a] The duration of anti-TNF treatment was calculated until the time tuberculosis was diagnosed or, for patients who did not develop tuberculosis, until the end of the follow-up period

of tuberculin skin test in patients already receiving immunosuppressive treatment. One such patient also developed tuberculosis, but she had fibrotic scars on the chest radiogram, despite being tuberculin-negative.

There may be several explanations for the development of active tuberculosis during TNF inhibitor therapy despite prior LTBI treatment. First, although we performed face-to-face interviews with the patients and tried to ensure the correctness of their answers, their adherence to INH treatment may have been suboptimal. We have tried to confirm our findings with the patients' records at the local tuberculosis dispensaries, which are officially in charge of providing anti-tuberculosis drugs and of following up all tuberculosis treatments. The records indicated that four of the patients were adherent with and completed their treatment. However, we were not able to find the related records of three patients and thus cannot firmly claim that they had been fully adherent to the LTBI treatment. Second, despite the fact that none of the patients reported any recent contact with patients with active tuberculosis, unknown or unnoticed contacts may have occurred. Third, other risk factors for tuberculosis identified in previous Turkish studies, including biomass use [21] and lower body mass index [22], may have been associated with the development of tuberculosis in these patients, but these two parameters were not recorded in the study database. Fourth, only INH monotherapy is given for LTBI treatment in Turkey and INH resistance may be a problem. However, none of the four patients with pulmonary tuberculosis and with positive cultures was found to have INH resistance.

The guidelines recommend yearly repeat screening of LTBI in patients who are initially found not to be infected [7]. No such recommendation has been made for patients who have already been documented to have LTBI and received the appropriate treatment; it has been argued that serial IGRA testing may be of help in identifying patients who have a high likelihood of reactivation or of new acquisition [23, 24]. However, serial IGRA testing may not be ideal (and has not been recommended in healthcare workers) because of the problems in defining an appropriate cut-off point, variability, and frequently observed conversions and reversions [25, 26].

Apart from the previous Turkish studies, another retrospective study from Greece showed that in 11 patients who developed anti-TNF-alpha-associated tuberculosis, seven patients had received or were receiving INH treatment, but that there was a high rate (20%) of failure to complete the treatment [27].

Previous studies have identified different risk factors for the development of tuberculosis, including Behçet's disease and tuberculin reaction of less than 10 mm (9), use of adalimumab, male sex and previous history of tuberculosis (10), use of infliximab, and LTBI teatment shorter than 9 months [28]. No risk factors have been identified in this study; however, similarly to previous studies, it showed that tuberculosis mostly developed in tuberculin-positive patients despite having been appropriately treated for LTBI. Thus, apart from regular follow-up of tuberculin-negative patients with annual tuberculin testing to detect new infections, a similar strategy may be adopted for tuberculin-positive patients. These patients need to be followed up more closely, perhaps also with annual tuberculin tests and/or IGRA for a period of 5 years, to gain more insight into the risk for developing active tuberculosis despite preceding LTBI treatment and to improve our approach to prevent tuberculosis.

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Author contribution YK and ASa conceived and prepared the study protocol and the database; YK, MNT, FO, and KA reviewed the patients' records and gathered the relevant data; YK and ASa interviewed the patients; YK and ASu analyzed the data; ASa and YK wrote the draft of the manuscript; and all authors reviewed the draft and contributed to the final version of the manuscript.

Data availability All presented data are available in the patients' hospital records and will be presented if required.

Code availability Not applicable.

Declarations

Disclosures None.

Ethics approval The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval no: 18-10/23) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patients gave informed consent for their clinical data to be used in this study.

Consent to participate All tuberculosis patients gave written informed consent to participate in the study.

Consent for publication All authors attest to the validity of the data and give consent to their publication.

References

1. Sayiner A, Ece T, Duman S, Yildiz A, Ozkahya M, Kiliçaslan Z, Tokat Y (1999) Tuberculosis in renal transplant recipients. Transplantation 68:1268–1271
2. Brassard P, Kezouh A, Suissa S (2006) Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 43:717–722
3. Arkema EV, Jonsson J, Baecklund E, Bruchfeld J, Feltelius N, Askling J, on behalf of the ARTIS Study Group (2015) Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments. Ann Rheum Dis 74: 1212–1217
4. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO (2004) Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 38:1261–1265

5. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ, Gabrielli EM, Lonati AC, Moja L, Cinquini M, Marino V, Matucci A, Milano GM, Tocci G, Scarpa R, Goletti D, Cantini F (2016) Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis and ankylozing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 15: 11–34
6. Xie X, Li F, Chen JW, Wang J (2014) Risk of tuberculosis infection in anti-TNF-alpha biological therapy: From bench to bedside. J Microbiol Immunol Infect 47:268–274
7. Turkish Ministry of Health, Department of Public Health (2019) Guidelines for the diagnosis and treatment of tuberculosis (in Turkish). https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/haberler/Tuberkuloz_Tani_Ve_Tedavi_Rehberi_/Tuberkuloz_Tani_ve_Tedavi_Rehberi_08.07.2019_Yuksek_KB.pdf. Accessed 18 December 2020
8. British Thoracic Society Standards of Care Committee (2005) BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to anti-TNF-alpha treatment. Thorax 60:800–805
9. Borekci S, Atahan E, Yilmaz DD, Mazıcan N, Duman B, Ozguler Y, Müsellim B, Hamuryudan V, Ongen G (2015) Factors affecting the tuberculosis risk in patients receiving anti-tumor necrossi factor-alpha treatment. Respiration 90:191–198
10. Cagatay T, Bingol Z, Kıyan E, Yegin Z, Okumus G, Arseven O, Erkan F, Gülbaran Z, Erelel M, Ece T, Cagatay P, Kılıcaslan Z (2018) Follow-up of 1887 patients receiving tumor necrosis factor-alpha antagonists: tuberculin skin test conversion and tuberculosis risk. Clin Respir J 12:1668–1675
11. Ergun T, Seckin D, Bulbul EB, Onsun N, Ozgen Z, Unalan P, Alpsoy E, Karakurt S (2015) The risk of tuberculosis in patients with psoriasis treated with anti-tumor necrosis factor agents. Int J Dermatol 54:594–599
12. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, on behalf of the BIOBADASER Group (2003) Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk. Arthritis Rheum 48:2122–2127
13. Jung YJ, Lee JY, Jo KW, Yoo B, Lee CK, Kim YG, Yang SK, Byeon JS, KİM KJ, Ye BD, Lee KH, Lee SD, Kim WS, Kim DS, Shim TS (2014) The "either test positive" strategy for latent tuberculous infection before anti-tumour necrosis factor treatment. Int J Tuberc Lung Dis 18:428–434
14. Kim HC, Jo KW, Jung YJ, Yoo B, Lee CK, Kim YG, Yang SK, Byeon JS, Kim KJ, Ye BD, Shim TS (2014) Diagnosis of latent tuberculosis infection before initiation of anti-tumour necrosis factor therapy using both tuberculin skin test and QuantiFERON-TB Gold in Tube assay. Scand J Infect Dis 46:763–769
15. Bonfiglioli KR, Ribeiro AC, Moraes JC, Saad CG, Souza FH, Calich AL, Bonfa E, Laurindo IM (2014) LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. Int J Tuberc Lung Dis 18:905–911
16. Debeuckelaere C, De Munter P, Van Bleyenbergh P, De Wever W, Van Assche G, Rutgeerts P, Vermeire S (2014) Tuberculosis infection following anti-TNF therapy in inflammatory bowel disease, despite negative screening. J Crohns Colitis 8:550–557
17. Hanta I, Ozbek S, Kuleci S, Kocabas A (2008) The evaluation of latent tuberculosis in rheumatologic diseases for anti-TNF therapy: experience with 192 patients. Clin Rheumatol 27:1083–1086
18. Akyuz F, Cavus B, Iliaz R, Soyer OM, Ormeci A, Evirgen S, Onder S, Koksalan K, Keskin M, Karaca C, Demir K, Gulluoglu M, Cagatay T, Besisik F, Kaymakoglu S (2019) Inflammatory bowel disease and mycobacteria: how much can we trust isoniazid prophylaxis during antitumor necrosis factor therapy ? Eur J Gastroenterol Hepatol 31:777–780
19. Busquets-Perez N, Ponce A, Ortiz-Santamaria V, de Agustin de Oro J, Hernandez-Rico YL, Vidal I, Alfonso C, Argemi S, Munoz B, Quispe F, Diaz AC, Campos S, Hernandez TM, Torres M, Suris X (2017) How many patients with rheumatic diseases and TNF inhibitors treatment have latent tuberculosis. Rheumatol Clin 13:282–286
20. Munoz L, Casa S, Juanola X, Bordas X, Martinez C, Santin M, for the Prevention of Anti-TNF-Associated Tuberculosis Study Team of Bellvitge University Hospital (2015) Prevention of anti-tumor necrosis factor-associated tuberculosis: a 10-year longitudinal cohort study. Clin Infect Dis 60:349–356
21. Gulhan PY, Elverisli MF, Ercelik M, Aytekin M, Balbay O, Arbak P (2020) Relationship between diagnosis period and internal and external air quality in patients with tuberculosis. Eurasian J Med 52: 77–80
22. Ceylan E, Karkucak M, Coban H, Karadag M, Yakut T (2017) Evaluation of TNF-alpha gene (G308A) and MBL2 gene codon 54 polymorphisms in Turkish Patients with tuberculosis. J Infect Public Health 10:774–777
23. Sauzullo I, Mengoni F, Marocco R, Potenza C, Skroza N, Tieghi T, Lichtner M, Vullo V, Mastroianni CM (2013) Interferon-gamma release assay for tuberculosis in patients with psoriasis treated with tumour necrosis factor antagonistis: in vivo and in vitro analysis. Br J Dermatol 169:1133–1140
24. Lee CK, Wong SHV, Lui G, Tang W, Tam LS, Ip M, Hung E, Chen M, Wu JC, Ng SC (2018) A prospective study to monitor for tuberculosis during anti-tumour necrosis factor therapy in patients with inflammatory bowel disease and immune-mediated inflammatory diseases. J Crohns Colitis 12:954–962
25. Stout JE, Belknap R, Wu YJ, Ho CS (2018) Paradox of serial interferon-gamma release assays: variability width more important than specificity size. Int J Tuberc Lung Dis 22:518–523
26. Bastian I, Coulter C, the National Tuberculosis Advisory Committee (NTAC) (2017) Position statement on interferon-gamma release assays for the detection of latent tuberculosis infection. Commun Dis Intell Q Rep 41:E322–E336
27. Sichletidis L, Settas L, Spyratos D, Chloros D, Patakas D (2006) Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 10:1127–1132
28. Kisacik B, Pamuk ON, Onat AM, Erer SB, Hatemi G, Ozguler Y, Pehlivan Y, Kilic L, Ertenli I, Can M, Direskeneli H, Keser G, Oksel F, Dalkilic E, Yilmaz S, Pay S, Balkarli A, Cobankara V, Cetin GY, Sayarlioglu M, Cefle A, Yazici A, Avci AB, Terzioglu E, Ozbek S, Akar S, Gul A (2016) Characteristics predicting tuberculosis risk under tumor-necrosis factor-alpha inhibitors: report from a large multicenter cohort with high background prevalence. J Rheumatol 43:524–529